**Figure 1**

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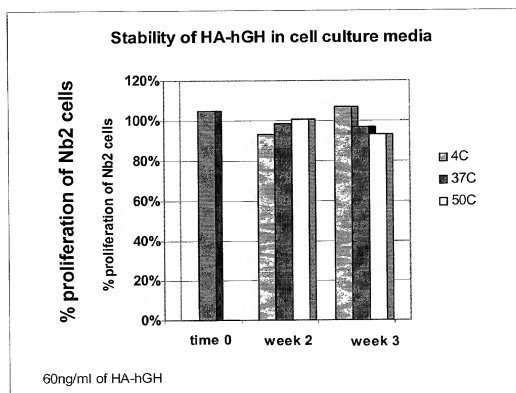


Figure 2

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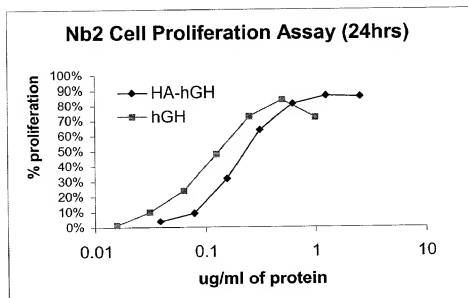


Figure 3A

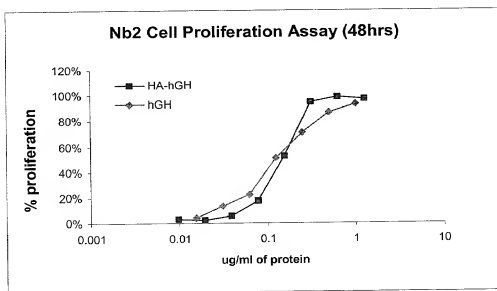


Figure 3B

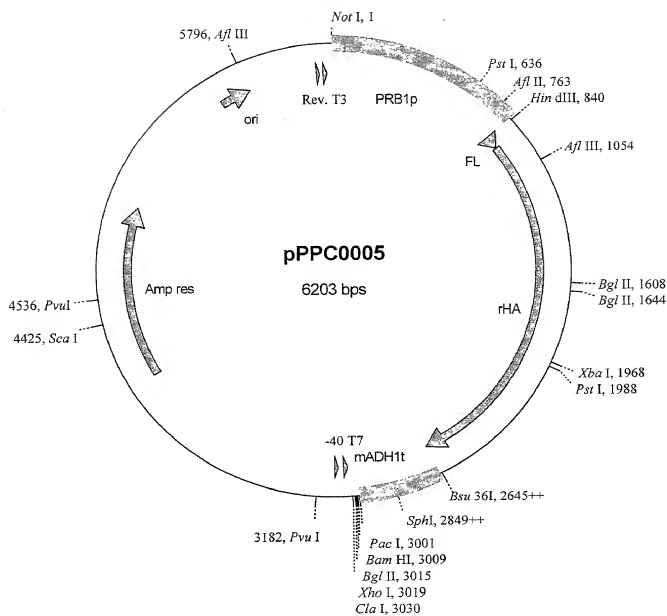


Figure 4

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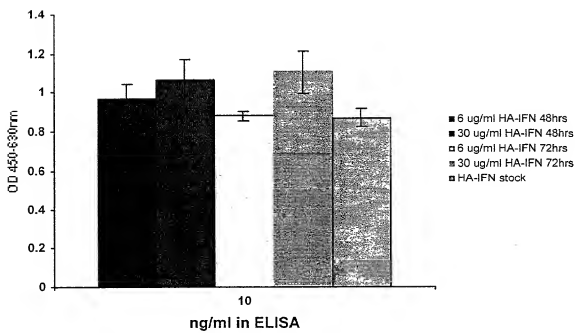


Figure 5

Figure 6

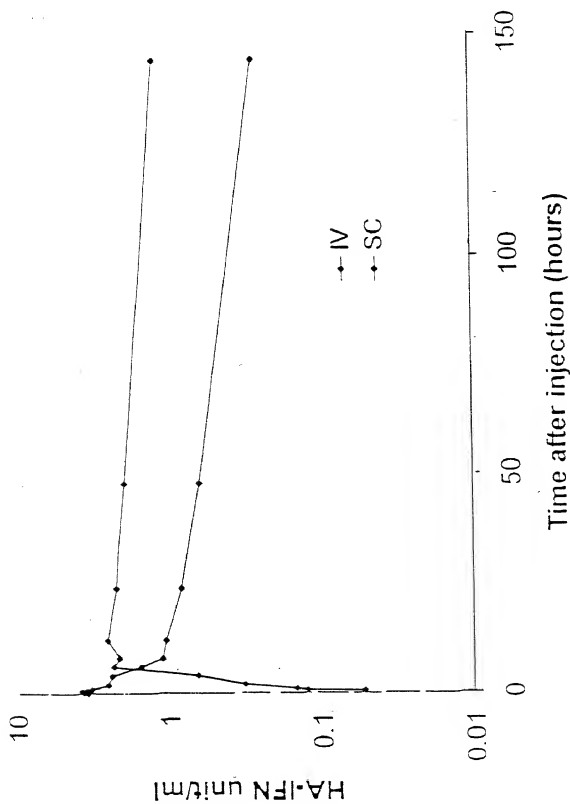
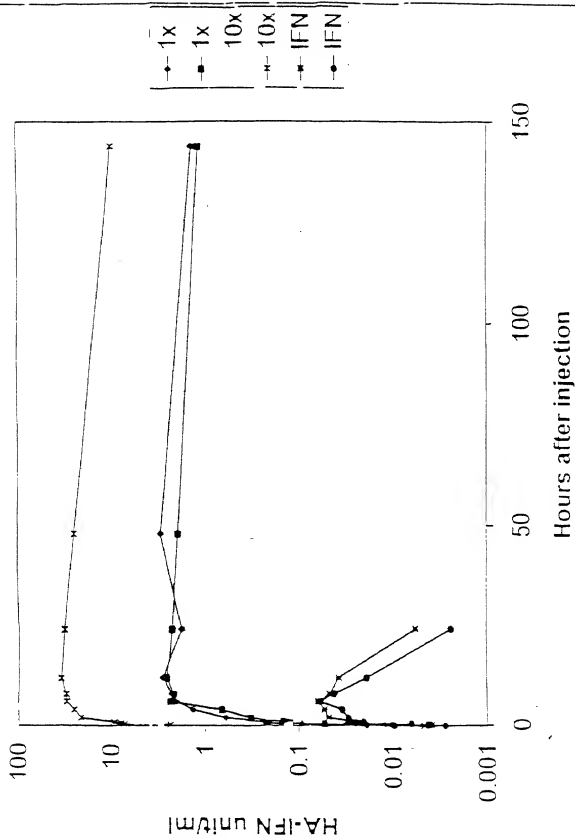


Figure 7



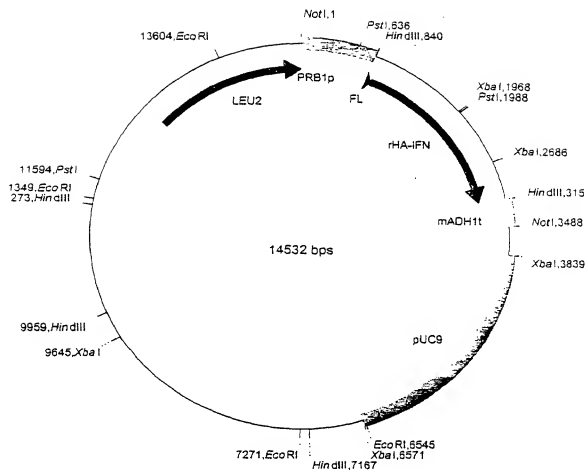


Figure 8. The HA-IFN α expression cassette in pSAC35. The expression cassette comprises

PRB1 promoter, from *S. cerevisiae*.

Fusion leader, first 19 amino acids of the HA leader followed by the last 6 amino acids of the MF α -1 leader.

HA-IFN α coding sequence with a double stop codon (TAATAA)

ADH1 terminator, from *S. cerevisiae*. Modified to remove all the coding sequence normally present in the *Hind III/BamHI* fragment generally used.

Figure 8

Localisation of 'Loops' based on the HA Crvstal Structure
which could be used for Mutation/Insertion

1	DAHKSEVAHR	FKDLGEENFK	ALVLIAFAQY	LQCCPFEDHV	KLVNEVTEFA
	HHHHH	HHH	HHH	HHHHH	HHHHHHHHHH
	I			II	
51	KTCV ADES AE	NCDKSLHTLF	GDKLCTVATL	RTY GEM ADC	CAKOE PER NE
	HHHHH	HHHHH	HHHHH	HHHH	H HHHH
101	CFLQHKDDNP	NLPRLVRPEV	DVMCTAFHDN	EETFLKKYLY	ELARRHPYFY
	HHHH	H	HHHHHHHH	HHHHHHHHHH	HHHHH
	IV				
151	APELLFFAKR	YKAA TECCO	AADKAA CLLP	KLDEL RDEGK	ASSAK QRLKC
	HHHHHHHHHH	HHHHHHHHHH	HHHHH	HHHEHHHHHH	HHHHHHHHHH
	V				
201	ASLQKFGERA	FKAWAVARLS	QRFPKAEFAE	VSKLVTDLTK	VHTECC HGDL
	HHHHH	HH	HHHHHHHHHH	HH	HHH HHHHHHHHHH
	VI		VII		
251	LECADDRADL	AKYIC ENODS	ISSK LKECCE	KPL LKESHCI	AEV END EMPA
	HHHHHHHHHH	HHHHH	HHHHH	HHHHHHH	H
301	DLP SLA ADFV	ESKD VC KNYA	EAKDVFLGMF	LYEYARRHPD	YSV LL LRLA
	HHHH	HHHHHH	HHHHHHH	HHHHHH	HHHHHHHH
	VIII				
351	KTYET TL LEKC	CAAAD PHECY	AKV F DEFKPL	VEEPQ N LIQ	NCEL F EQLGE
	HHHHHHHHHH	HH	H	HHHHH	HHHHHHHHHH
	IX				
401	YKFQ N ALLVR	YTKK VP QVST	PTLVE VS RNL	GKVGSKC CKH	PEAK R MPCAE
	HHHHHHHHHH	HHHH	H	HHHHHHHHHH	HHH
	X		XI		
451	DYLSV VL NQL	CVL HEK TPVS	DRV T KCCTES	LVNRR PP CFSA	LEVDE T YVPK
	HHHHHHHHHH	HHHHH	HHHHHHHHH	HHHHHHHH	
501	EFNAETFTFH	ADICTLSEKE	RQIKKQTALV	ELVKHKPKAT	KEQLKAVMD
		HHH	HHH	HHHHMMEH	HHH
	XII				
551	FAAFVEK CKCK	ADD KET CFAE	EGKKLVAA SQ	AALGL	
	HHHHHHHH	HHHH	HHHHHHHHHH	HH	
	Loop				
	I	Val54-Asn61	VII	Glu280-His288	
	II	Thr76-Asp89	VIII	Ala362-Glu368	
	III	Ala92-Glu100	IX	Lys439-Pro447	
	IV	Gln170-Ala176	X	Val462-Lys475	
	V	His247-Glu252	XI	Thr478-Pro486	
	VI	Glu266-Glu277	XII	Lys560-Thr566	

Figure 9

Examples of Modifications to Loop IV**a. Randomisation of Loop IV.**

IV
 151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

IV
 151 APELLFFAKR YKAAFTECCX XXXXXXCLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

b. Insertion (or replacement) of Randomised sequence into Loop IV.

(X)_n



IV

151 APELLFFAKR YKAAFTECCQ AADKAACLLP KLDEL RDEGK ASSAKQRLKC
 HHHHHHHHHH HHHHHHHHHH HHHHH HHHHHHHHHHH HHHHHHHHHHH

The insertion can be at any point on the loop and the length a length where n would typically be 6, 8, 12, 20 or 25.

Figure 10

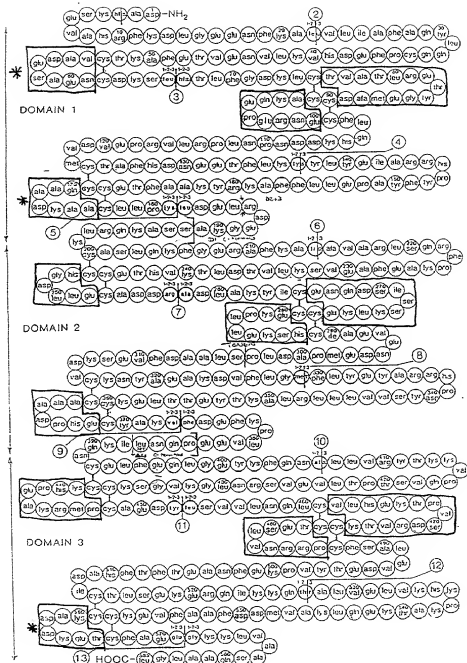
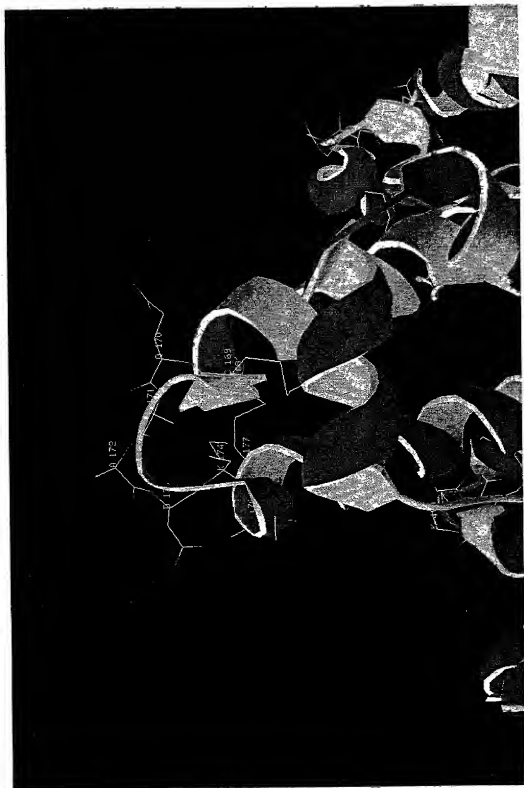


Figure 11



Disulfide bonds shown in yellow

Figure 12: Loop IV Gln170-Ala176



Figure 13: Tertiary Structure of HA

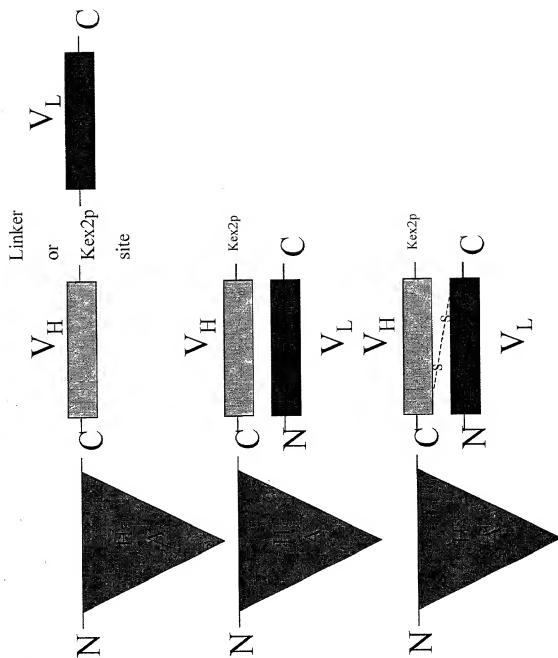


Figure 14: Schematic Diagram of Possible ScFv Fusions
 (Example is of a C-terminal fusion to HA)

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1	GAT	GCA	CAC	AAG	ACT	GAG	GTT	GCT	CAT	CGG	TTT	AAA	GAT	TTG	GGA	GAA	AAT	TTC	AAA	60	
1	D	A	H	K	S	E	V	A	H	R	F	K	D	L	G	E	N	F	K	20	
61	GCC	TTG	GTG	TTG	ATT	GCC	TTT	GCT	CAG	TAT	CTT	CAG	CAG	TGT	CCA	TTT	GAA	GAT	CAT	GTG	120
21	A	L	V	L	I	A	F	A	Q	Y	L	Q	Q	C	P	F	E	D	H	V	40
421	AAA	TTA	GTG	AAT	GAA	GTG	ACT	GAA	TTT	GCA	AAA	ACA	TGT	TTT	GCT	GAT	GAG	TCA	GCT	GAA	180
41	K	L	V	N	E	V	T	E	F	A	K	T	C	V	A	D	E	S	A	E	60
181	AAT	TGT	GAC	AAA	TCA	CTT	CAT	ACC	CTT	TTT	GGA	GAC	AAA	TTA	TGC	ACA	GTT	GCA	ACT	CTT	240
61	N	C	D	K	S	L	H	T	L	F	G	D	K	L	C	T	V	A	T	L	80
241	CGT	GAA	ACC	TAT	GTT	GAA	ATG	GCT	CAC	TGC	TGT	GCA	AAA	CAA	GAA	CCT	CAG	AGA	AAT	GAA	300
81	R	E	T	Y	G	E	M	A	D	C	C	A	K	Q	E	P	E	R	N	E	100
301	TGC	TTT	TTG	GAA	CAC	AAA	GAT	GAC	AAC	CCA	CTC	CCC	GGA	TTG	GTG	AGA	CCA	GAG	GTT	360	
101	C	F	L	Q	H	K	D	N	P	N	L	P	R	L	V	R	P	E	V	120	
361	GAT	GTG	ATG	TGC	ACT	GCT	TTT	CAT	GAC	AAT	GAA	GAG	ACA	TTT	TTG	AAA	AAA	TAC	TTA	TAT	420
121	D	V	M	C	T	A	F	H	D	N	E	E	T	F	L	K	K	Y	L	Y	140
421	GAA	ATT	GCC	AGA	AGA	CAT	CCT	TAC	TTT	TAT	GCC	CGC	GAA	CTC	CTT	TTT	GCT	AAA	AGG	480	
11	E	T	A	R	H	P	Y	F	Y	A	P	E	L	L	F	F	A	K	R	160	

481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC TGC CTG TTG CCA 540
 161 Y K A A F T E C C Q A A D K A A C L L P 180

 541 AAG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAG AGA CTC AAA TGT 600
 181 K L D E L R D E G K A S S A K Q R L K C 200

 601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGC CTG AGC 660
 201 A S L Q K F G E R A F K A W A V A R L S 220

 661 CAG AGA TTT CCC AAA GCT GAT TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720
 221 Q R F P K A E F A E V S K L V T D L T K 240

 721 GTC CAG ACG GAA TGC TGC GAT GGA GAT CTG CTT GAA TGT GCT GAT GAC AGG GCG GAC CTT 780
 241 V H T E C C H G D L L E C A D D R A D L 260

 781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 840
 261 A K Y I C E N Q D S I S S K L K E C C E 280

 841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900
 281 K P L L E K S H C I A E V E N D E M P A 300

 901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960
 301 D L P S L A A D F V E S K D V C K N Y A 320

Figure 15B

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961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020
 321 E A K D V F L G M F L Y E Y A R R H P D 340

1021 TAC TCT GTC GTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080
 341 Y S V V L L L R L A K T Y E T L E K C 360

1081 TGT GCC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140
 361 C A A A D P H E C Y A K V F D E F K P L 380

1141 GTG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200
 381 V E E P Q N L I K Q N C E L F E Q L G E 400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA CTA CCC CAA GTG TCA ACT 1260
 401 Y K F Q N A L L V R Y T K K V P Q V S T 420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320
 421 P T L V E V S R N L G K V G S K C C K H 440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 1380
 441 P E A K R M P C A E D Y L S V V L N Q L 460

1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440
 461 C V L H E K T P V S D R V T K C C T E S 480

Figure 15C

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1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500
481 L V N R R P C F S A L E V D E T Y V P K 500

1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
501 E P N A R T F T F H A D I C T L S E K E 520

1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
521 P O I K K O T A L V E L V K H K P K A T 540

1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GGT TTT GTA GAG AAG TGC TGC AAG 1680
541 K E O L K A V M D D F A A F V E K C C K 560

1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
561 A D D K F T C F A E E G K K L V A A S Q 580

1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
581 A A I G I *

Figure 15D